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NAVY DEPARTMENT

BUMED NEWS LETTER

a digest of timely information

Editor - Captain F. W. Farrar. (MC). U.S.N.

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ATTENTION, RESERVE MEDICAL OFFICERS

To

"OPERATION NAVAL RESERVE"

Week of 18 to 25 May 1947

OPERATION NAVAL RESERVE is a Naval Reserve recruiting publicity program which the Navy considers to be of major importance in the reactivation of the Naval Reserve.

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Mechanism of the Invasiveness of Cancer: In contrast to benign tumor cells, which remain restricted to their site of origin, malignant cells have the ability to infiltrate adjacent tissues and thus become locally disseminated. Furthermore, the capacity of malignant cells for invasiveness allows them to penetrate into the lumens of lymphatic and blood vessels, whereby they are transported to more distant parts.

Because it was thought that physical and chemical differences must exist between benign and malignant neoplastic cells which permit the former to remain localized and the latter to permeate adjacent normal tissues, the Department of Pathology of the University of Pennsylvania Medical School during the last several years has made studies designed to explain the mechanism of the invasiveness of malignant tumors.

The Decreased Adhesiveness of Cancer Cells. It was demonstrated by the author that attached pairs of cancer cells could be separated from each other by micromanipulation through the application of much less force than was required to separate normal or benign tumor cells. The mutual adhesiveness of the cells was determined by measuring the bend produced in a previously calibrated microneedle when subjected to the strain of detaching one cell from another. Thus, it was found that the mean force required to separate 50 pairs of normal squamous epithelial cells obtained from the lip was 1.42 mg. Similarly, the value of adhesiveness for cells from skin papillomas was 1.25 mg. On the other hand, the mean force necessary to separate 50 pairs of cells from squamous cell cancers of the lip was only one-third this value, or 0.47 mg.

It is difficult to visualize any mechanism of invasiveness if tumors are composed of compact masses of tightly adherent cells. However, if the cells are but feebly attached to one another, facilitating complete separation, such separated cells are free to wander into adjacent parts by ameboid movement.

Attempts were then made to find a chemical explanation of reduced adhesiveness. Normal squamous epithelial cells were subjected to various alterations in the chemical composition of the medium in which they were immersed while their adhesiveness was measured. In this way it was shown that absence of calcium from the medium caused reduction in adhesiveness of the cells. For example, the mean force required to separate 100 pairs of cells in balanced salt solution was 1.34 mg., whereas the value for cells in calcium-free salt solution was only 0.96 mg., a significantly lower value.

Since it has also been shown by A. Brunschwig, L. Dunham, and S. Nichols that cancerous tissue is abnormally low in calcium, and since the investigations have indicated that adhesiveness of normal cells was decreased when calcium

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was lowered experimentally, it was concluded that the decreased adhesiveness of cancer cells of the squamous epithelial variety is dependent upon their low calcium content.

The Ameboid Movement of Cancer Cells. A satisfactory chemical basis for separation of cancer cells from each other having been found, the only additional requisite for invasiveness is the ability of the detached cells to move; that is, if the cells, no longer bound to each other, are capable of ameboid movement, their penetration of the adjacent tissues is understandable. In observations of epithelial cells from human carcinomas in tissue culture, it was found that individual cells frequently became detached from outgrowing sheets or clusters of this cancerous epithelium and, further, that these detached cells were actively ameboid. Cells were seen to move some distance from the cluster from which they were derived and, by their proliferation, to build up new colonies. These observations confirmed earlier reports of ameboid movement in cells from both sarcomas and carcinomas. Thus, it can be regarded as established that, once cancer cells have become detached, they are capable of ameboid motion.

The Role of Spreading Factors. The detached malignant cell with ameboid motility is physically adapted to invade surrounding tissues. It was considered possible that cancer cells in some way cause the permeability of normal tissue to be increased. This suggested the hypothesis that malignant tumors contain spreading factors, such as hyaluronidase, which, by softening the intercellular cement substance of adjacent normal tissues, render these tissues more susceptible to penetration by cancer cells.

Experiments were designed to test this hypothesis. It was found that several of the malignant tumors examined did contain spreading factors. In most instances the spreading factor content was not great, and in some it was lacking. When considering the presence of spreading factors in malignant tissues, it must be emphasized that the source of the spreading factors within the tumors has not been determined. It is possible that hyaluronidase was present in certain tumors because of infection by bacteria which were the source of the enzyme. If this is the only source of hyaluronidase in malignant tissue, then its presence is coincidental, even though it conceivably operates to facilitate invasion by the tumor cells by rendering the adjacent tissues more susceptible to penetration. It has yet to be demonstrated that the cancer cell itself contains hyaluronidase. Regardless of the source of the spreading substance, in several instances, this analysis of human tumors revealed significant amounts present, so that support is lent to the hypothesis that spreading factors may facilitate the invasiveness of cancer cells.

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In order to determine whether an excess of hyaluronidase would increase the invasiveness of tumors, hyaluronidase was injected into transplantable sarcomas in mice, and into virus-induced papillomas in rabbits. The mouse sarcomas were invasive and metastasized to the lungs. It was thought that if hyaluronidase increased the invasiveness of these sarcomas, there would be earlier establishment of the tumors and an increased frequency of pulmonary metastases. No indications of augmented invasiveness were demonstrable. The rabbit papillomas are primarily benign tumors which may become malignant in some instances when allowed to grow for a long time. It was thought that local injection of hyaluronidase might increase the incidence of malignancy, as judged by invasiveness and distant metastases. Again, confirmative evidence was not obtained. The negative results in these experiments force the conclusion that spreading factors of the hyaluronidase type, though they may be found in malignant tumors, are not essential to invasiveness. The mouse tumors, for instance, were already strongly invasive, and their invasiveness apparently could not be enhanced by an excess of hyaluronidase experimentally introduced.

In these experiments, in which a spreading factor was injected into the animals daily over long periods, the formation of antienzymes must be considered. Such antienzymes, which inhibit the action of the enzyme on its substrate, have been reported, and it will be necessary to await further developments in this field before better experiments can be designed.

Of the three factors, decreased adhesiveness, ameboid movement, and spreading factor, the first two are of greater importance for invasive growth. It is of interest in this regard that the most invasive of all normal cells, macrophages, polymorphonuclear leukocytes, and lymphocytes, are all detached cells, rarely showing any evidence of mutual adhesiveness and all having great ameboid activity. The cancer cell possesses these same attributes, coupled with its characteristic of uncontrolled proliferation. (Science, April 4, '47 - D. R. Coman)

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The Antihistamine Compound Pyribenzamine in Skin Disorders: A new group of antihistamine compounds known chemically as pyridylethylenediamines has recently been prepared. One of them (N′ pyridil-N′ benzyl-N-dimethyl-ethylenediamine) was called pyribenzamine.

This drug neutralized the effects of histamine on an isolated strip of guinea pig intestine. It was found effective against histamine-induced asthma in guinea pigs and against anaphylactic shock produced by the injection of horse serum in

guinea pigs. The drug was also found effective against intratracheal injections of histamine in guinea pigs. Wheals produced by the intracutaneous injection of histamine in rabbits could be prevented by the intravenous administration of the drug or by gastric instillation. The drug was relatively nontoxic for white mice, white rats, and rabbits, and human beings tolerated the drug well. It was found that the drug protected against horse-serum anaphylaxis in dogs in 50 per cent of cases. The drug administered to white rats for a period of five months showed no deleterious effects on the erythrocytes, white cells, hematocrit values, body weight, appetite, reproductive capacities, gastro-intestinal functions, or general appearance.

From an experimental laboratory standpoint in a comparison of the action of pyribenzamine with that of benadryl, a compound known as "antergan" (dimethylaminoethylbenzylaniline), and two other antihistamine drugs it was apparent that pyribenzamine was superior, antergan was second, and benadryl was third.

In this study a total of 122 patients was given the drug, and of these, 89 were followed sufficiently long so that the effects of the drug could be evaluated.

Acute Urticaria -- Of 34 patients with acute urticaria treated from two to fourteen days with pyribenzamine, in dosages of from 100 to 400 mg. per day, the follow-up was satisfactory in 24. Twenty-three of these 24 patients obtained prompt and definite relief of symptoms. (Approximately the same percentage of patients obtained relief from benadryl). Nineteen of the 24 patients were improved 50 per cent within twenty-four hours, and free of urticaria in less than ten days. Four patients were at least 50 per cent improved in four days and free of eruption in fourteen days. In 3 of the latter 4, the urticaria returned twenty-four hours after the drug was stopped, but was controlled by readministration. The only failure in this group occurred in one patient with acute urticaria, believed to be due to codeine in cough syrup.

Chronic Urticaria -- Twenty-three patients with chronic urticaria were given pyribenzamine from six days to six months in dosages of from 200 to 300 mg. per day. Fifteen of these patients were followed adequately. Nine of the 15 were definitely benefited, whereas 6 patients reported no relief of symptoms. (This result is essentially the same as that obtained with benadryl.) In 6 of the 9 patients benefited by the drug, a recurrence of the urticaria developed within twenty-four hours after use of the drug was discontinued, but relief was again experienced when the drug was readministered. One patient had had urticaria for four months and took 200 mg. of pyribenzamine daily for fourteen days; the symptoms completely disappeared within forty-eight hours and have not recurred.

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Atopic Dermatitis (Investigative Studies) -- Sixteen patients with a chronic atopic dermatitis were studied in order to determine the effects of pyribenzamine on wheals resulting from the intradermal injection of a series of allergens. The allergens used were sheep wool, mixed feathers, milk, cat hair, and three dilutions of egg white. The wheals resulting from these intradermal injections were observed and measured at the end of fifteen minutes. Patients were then given 100 mg. of pyribenzamine and one hour later were retested with the same allergens as those which produced positive reactions in the original test. Of the 16 patients who received the intradermal injections, in 15, wheals developed to one or more of the allergens. In 7 of the 15, pyribenzamine produced no demonstrable diminution in the size of the wheal. Eight of the 15 showed a decrease in the size of the wheal of 33.3 per cent or more. Two of the 8 following the ingestion of pyribenzamine, had no wheals on the second series of tests. On the basis of these experiments, the outcome of the clinical use of pyribenzamine in these patients could not be predicted.

Chronic Atopic Dermatitis (Effect of Pyribenzamine on Symptoms) -- Thirty-five patients with chronic atopic dermatitis were given pyribenzamine in dosages of from 100 to 400 mg. daily for periods which varied from two weeks to four months. In the case of children, the dose varied in proportion to the body weight. Thirty of these patients were followed sufficiently long to determine the effects of pyribenzamine on the course of their disease. Nineteen of the 30 received definite relief of pruritus to the extent of at least 50 per cent. Three of the 19 experienced relief of pruritus within twenty-four hours. The remaining 16 patients were decidedly improved within a two-week interval. In 16 of the 19 patients, itching recurred when the drug was stopped and was again relieved when the drug was readministered. In 3 of the 19 patients, the dermatitis disappeared within six weeks and has not recurred to date. It must be stated that all these patients received the usual routine treatment with topical applications and advice regarding the avoidance of common water-soluble protein allergens. Some patients deliberately stopped taking the drug or their supply ran out, and these patients felt that there was a prompt flare-up of the itching. Four of the 7 patients who showed no change in allergen-induced wheals after receiving 100 mg. of pyribenzamine were adequately followed. In 3 of these the pruritis was improved at least 50 per cent while taking the drug, and in one of these the eruption disappeared fifteen days after medication was started. There was, therefore, no correlation between the effects of pyribenzamine on allergen-induced wheals and clinical improvement. It was further noted that in the case of the 8 patients in whom pyribenzamine definitely diminished the size of the allergen-induced wheals, only 4 of these were benefited while taking the drug. This further demonstrated the lack of correlation between the effects of the drug on allergen-induced wheals and the results obtained clinically from the administration of the drug. The authors believe that pyribenzamine is definitely palliative for approximately two-thirds of the patients with chronic atopic dermatitis.

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Dermatitis Venenata -- Fifteen patients with dermatitis venenata of long duration, most of whom were originally patients with industrial dermatitis, were given pyribenzamine in amounts up to 400 mg. per day. In none of these did the drug appear to influence in any way the course of the eruption, nor did it produce any relief of symptoms.

Physical Allergy -- Two of the best results were in patients who presented examples of severe physical allergy of long duration. The first patient was a woman 50 years of age who had had severe sunlight urticaria for eighteen years. She had received medical attention from outstanding internists and had received every form of therapy known to the authors and to many other consulting dermatologists. Laboratory studies of every conceivable type had given uniformly normal results. On a trip to Florida during the past winter, minimal exposure to bright sunlight produced the usual papular urticarial lesions. On each day thereafter, 100 mg. of pyribenzamine taken before and after exposing herself to sunlight for periods of from two to four hours completely prevented the development of urticarial lesions. Furthermore, the existing lesions, which usually healed in from ten to fourteen days, disappeared within from two to three days. Subsequent exposure to bright sunlight without pyribenzamine medication caused the usual urticarial lesions to appear. The second patient, a woman aged 53, had suffered from urticaria due to cold for thirty-three years. During this time, she had had countless episodes of giant urticaria involving all the exposed parts. Exposure to cold water, either in the tub or for purposes of swimming, had brought on collapse with loss of consciousness on three occasions. Numerous allergy tests and attempts at desensitization had given unsuccessful results. She had been unable to eat ice cream for thirty-three years. She had had as many as 22 injections of epinephrine in a twenty-four hour period. Tests with small ice cubes produced erythema after fifteen seconds and severe urticaria after thirty seconds. Following the ingestion of 100 mg. of pyribenzamine, tests with small ice cubes showed extremely slight erythema at thirty seconds and only slight urticaria after sixty seconds. This patient has had complete relief by taking from 50 to 100 mg. of pyribenzamine before exposing herself to cold in any form and for the first time in thirty-three years, she was able to eat a large dish of ice cream with impunity.

Dermatitis Herpetiformis -- Four patients with dermatitis herpetiformis received from 200 to 300 mg. of the drug daily. Three of the 4 patients had almost complete relief of pruritis and burning while taking the drug, and the eruption healed. After observation, however, the authors were not able to state that the relief was any greater than that experienced following the ingestion of sulfapyridine although it was much more prompt.

Miscellaneous Conditions -- One patient with rather extensive insect bites secured prompt relief from itching following the administration of pyribenzamine.

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Reactions to Pyribenzamine -- In this study reactions to pyribenzamine severe enough to be noted by the patient without suggestion were extremely rare. Questioning of the patients was purposely confined to one point, namely, whether they had noted unusual symptoms after the ingestion of the drug. Only 4 patients out of a total of 89 noted any disturbance. One patient complained of headache, another felt drowsy, one had nausea and the fourth had nausea and vomiting. The last patient was the only one that had to discontinue use of the drug, although he had taken it steadily for a period of four months. These figures regarding reactions are certainly at variance with those of some other workers. Part of this may be explained by the fact that the authors mostly employed smaller dosages. The authors believe from their own results, and in comparison with reported reactions from benadryl in the literature, that reactions from the use of pyribenzamine are considerably less than those after use of benadryl when given in comparable dosage in the same type of case.

In a discussion of this study, Dr. Hamilton Montgomery, Rochester, Minn. stated that his experience together with that of his colleagues in the Department of Dermatology of the Mayo Clinic is in agreement with and supports in the main what Doctor Osborne states about pyribenzamine. Doctor Brunsting has reported on a series of 215 patients with various dermatoses treated with pyribenzamine. It is the impression of Doctor Montgomery and his associates that pyribenzamine is slightly superior to benadryl, because, although dose for dose they act about the same, the side reactions from benadryl are more frequent and more severe than those from pyribenzamine. Doctor Brunsting's experience in cases of dermatitis venenata (contact dermatitis) differs from that of Doctor Osborne in that there were several cases in which there was some relief from the pruritis, but no significant influence was noted on the dermatitis per se. Five patients with dermatitis herpetiformis received no benefit from pyribenzamine. In patients in the early phases of acrosclerosis (scleroderma and Raynaud's disease), with either benadryl or pyribenzamine Doctor O'Leary obtained moderate temporary improvement in approximately 25 per cent of the cases, resulting in relaxation of the skin and restoration of some of the lost function of the fingers and hands. Both drugs are effective in relieving the symptoms of pruritis from urticaria in from 85 to 90 per cent of the two series of cases. The response is usually symptomatic and palliative and requires continued use of the drugs; however, an occasional patient is encountered who is apparently cured of chronic urticaria after using either drug for several weeks. The same effects are noted in angioneurotic edema. Pyribenzamine has a beneficial effect in that it produces slight drowsiness, which in itself is beneficial in obtaining relaxation in cases of urticaria. In the group with atopic eczema, a small percentage has derived relief from the severe paroxysms of pruritus.

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In the discussion Dr. Marion B. Sulzberger of New York stated that there are just slight variations between their findings and those of Doctor Osborne and his collaborators. In the few patients with dermatitis herpetiformis treated they were not particularly impressed with the benefits. It may be, however, that when a larger series has been treated these differences in results will be ironed out. Also with adult atopic dermatitis they were not impressed, although an occasional patient did well. The impression was that the earlier the case and the younger the disease, the better the results with pyribenzamine. But this drug is by no means the answer to the control of this disease or even the control of itching in this eruption. Only an exceptional patient with atopic dermatitis does really well; a few patients get moderate or questionable benefit and many in their experience get no benefit whatsoever up to the limits of the tolerated doses. (Arch. Dermat. & Syph., March '47 - E. D. Osborne et al.)

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The Clinical Use of Globulin and Thrombin Preparations in Hemophilia: The beneficial effect of whole blood transfusion in hemophilia has been recognized for over 30 years. The marked fall in the coagulation time following the transfusion of normal blood was attributed in 1916 by Minot and Lee to the platelets. Patek and Stetson reinvestigated the problem in 1936. They confirmed the findings of Minot and Lee, but showed that plasma free of formed elements including blood platelets had an effect similar to that of whole blood and proposed the thesis that the beneficial effect of whole blood transfusion in hemophilia was due to a factor or factors residing in the blood plasma. The prolonged coagulation time in hemophilia was due in the opinion of these authors to a deficiency of the plasma factors.

In a series of studies reported from the Thorndike Memorial Laboratory over the past 12 years it has been shown that the antihemophilic property of platelet-free plasma is closely associated with the globulin fraction of the plasma proteins. It has also been shown that the antihemophilic factor is neither prothrombin nor fibrinogen. Globulin fractions of normal human plasma prepared free from both prothrombin and fibrinogen had optimal effect in reducing the prolonged coagulation time of hemophilic patients to normal both in vitro and in vivo.

During the war large quantities of the plasma globulins obtained as a by-product from the preparation of human albumin became available for physiologic study. In vitro studies of Cohn's fractions showed that Fractions I, II, and III had marked antihemophilic activity. Fraction IV had on occasion slight activity and Fraction V, the albumin fraction itself, had none.

Since it was known that Fraction I, that is, the fraction containing from 60 to 90 per cent of fibrinogen, could be injected into human beings, in vivo

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studies were commenced on this fraction. There is no implication that Fraction I is the best source of antihemophilic potency, but its availability in sterile dried form offered a convenient starting point for investigation. As little as 11 mg. of Fraction I injected intravenously into a patient with hemophilia caused a marked drop in the coagulation time, whereas amounts of between 200 and 400 mg. gave optimal effects. The injection of preparations of Fraction I were comparable in their antihemophilic effect with those obtained following the injection of whole blood or plasma.

The effect of Fraction I injected intramuscularly seems to be unpredictable when administered to adult patients even when massage and heat are used at the site of injection.

Fraction I contains the fibrinogen of blood plasma as well as small amounts of prothrombin. Since earlier work by the authors indicated that neither of these proteins was responsible for the antihemophilic properties of plasma, it was important to remove these substances from Fraction I. This step was accomplished by heating a solution of Fraction I to 56° C. for five minutes and filtering it. The filtrate contained no fibrogen and only traces of prothrombin. However, it was as effective in antihemophilic activity as the whole fraction from which it was prepared. This observation makes it probable that the antihemophilic property of plasma may be concentrated in a few milligrams of material, offering possibly an opportunity for a therapeutic approach to hemophilia.

At the present time two important matters must be clearly understood. The preparations of Fraction I vary a great deal in their antihemophilic potency. This can only be remedied after further study of the preparations in order to obtain satisfactory criteria. Secondly, as increased purity is obtained, some cases of hemophilia fail to respond to the injection of Fraction I although they respond to crude preparations of plasma proteins and to plasma. It has been assumed for some years that the deficiency in hemophilia is not necessarily a single factor. Therefore, as soon as suitable preparations for intravenous human use are obtained, other of the globulin fractions must be investigated in patients who fail to respond to Fraction I.

The injection of Fraction I may be used in the preparation of patients with hemophilia for dental extraction. The use of Fraction I for the control of hemorrhage in hemophilia is under investigation. A much more extensive clinical trial is necessary to evaluate the usefulness of the preparation for this purpose although the results so far have been promising. No refractory phase has been obtained following the injection of Fraction I and no deleterious reactions following the injection of the material have been observed. The dose of the material required to control hemorrhage varies from patient

to patient. At present 400 mg. of the material in 20 c.c. of isotonic salt solution is used as an initial dose. In preparing patients for operative procedures multiple injections may be employed on the day preceding the operation. However, if the patient is already anemic due to repeated hemorrhage, it is essential that whole blood be used rather than only plasma or antihemophilic globulin.

Of equal importance to the control of the blood coagulation time in hemophilia is the control of local hemorrhage when it occurs. The availability of a good hemostatic agent for this purpose is desirable. Antihemophilic globulin has some hemostatic properties. However, since this material produces clotting of blood by activating the blood coagulation reaction, its effects require a matter of minutes to develop. On the other hand, thrombin preparations which act directly on fibrinogen to produce fibrin clots require only seconds to produce this effect. For this reason, thrombin is an ideal hemostatic agent.

As Doctor Cohn has pointed out, preparations rich in prothrombin can be obtained by suitable fractionation of the plasma globulins. Prothrombin can be converted to thrombin by interaction with tissue thromboplastin derived from brain, lung, placenta or other tissues. The thrombin so obtained may be spread on or impregnated into sterile gauze, fibrin foams or absorbable cellulose and applied with pressure to the bleeding point. It is important that the highest possible concentration of thrombin be applied to the lesion. For this reason the authors favor the direct application of packs containing powdered thrombin rather than liquid preparations which may wash away rather quickly from the wound. Preparations of human thrombin and absorbable nonreactive sponges are of importance for use in wounds which later are to be closed by suture. For open local hemostasis thrombin from animal sources may be employed.

For some years, the authors have applied animal thrombin locally to wounds with no resulting local or systemic sensitivity reactions.

A thrombin preparation requiring no activation with thromboplastin has been made by Parfentjev from rabbit plasma by simple salting-out procedures. The authors have made similar preparations from the plasma of swine, steers, and human beings. This preparation is available under the commercial name of "Hemostatic Globulin" and is an extremely potent hemostatic agent. Thrombin preparations must never be injected parenterally due to the fact that they can produce intravascular clotting and profound shock.

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The availability of thrombin preparations has reduced enormously the risk of surgical procedures among hemophilic patients. With the use of thrombin over the past ten years in the authors' hemophilic clinic, bleeding has been well controlled following operative procedures, such as dental extractions, amputation, and skin grafting, and no serious sequelae have developed.

Further progress is to be expected in the development of therapeutic agents for the treatment of hemophilic hemorrhage. Standardization of the commercial methods for the production of antihemophilic preparations is required, and a careful assay of the in vivo activity of other fractions is necessary. (Ann. Int. Med., March '47 - G. R. Minot and F. H. L. Taylor)

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Temperature Equalization for the Relief of Pain: The effects of temperature on pain have not been adequately studied, yet the use of heat for its analgesic properties is everyday practice in medicine. The author, H.S. Wells, working in the Department of Physiology of the University of Minnesota, considered that if the action of heat on pain were understood, methods of treatment could probably be improved.

The simple observations reported point to a clearcut explanation of some of the relations of pain to temperature. Although most of the studies were carried out on one normal subject (the author), confirmation of important findings has been obtained on other subjects. It is realized that the validity of any study of the subjective phenomena of pain must rest chiefly on general confirmation by many observers. The exact interpretation of the findings may be considered tentative, for, although the hypothesis formulated is the only concept which seems to fit the facts so far determined, it will need further experimental support, especially of a quantitative nature.

Observations on Pain Produced by a Spring Clamp: If a metal spring-type artery clamp is applied to the finger web, moderate pain results, which will be lessened or even abolished by warming the hand and clamp in air or water. This result is obtained even when blood flow to the arm is stopped completely by inflation of a sphygmomanometer cuff to 200 mm. of mercury.

It is found, further, that warming the hand by means of a heat lamp fails to relieve the pain if the clamp and clamped tissue at the same time are kept cool by dipping the projecting metal in water at the initial skin temperature of the hand. Similarly, warming of larger areas of the body fails to relieve the pain. It is concluded that the effects of heating are local and direct and

due neither to vague, psychologic effects of warmth nor to an effect of warmth on pain impulses at the spinal level.

If the hand is maintained at its original temperature but the end of the clamp is dipped in water at from 34° to 37°C., pain is relieved. Warming the clamp and clamped tissue above 37° or 38°C., however, causes a return of pain and/or an increase of its intensity as warming is carried up to 45°C., above which point tissue is injured and pain will occur even in the absence of other injury. Since the optimum temperature for the relief of pain by heating is approximately that of the blood and deep tissues, the idea suggests itself that it may be not the heating per se which stops the pain but rather the equalization of superficial and deep tissue temperatures. Confirmation of this idea appears from other types of experiments to be described.

If the clamp, while producing moderate pain, is dipped into cool water, e.g., 20°C., the pain is notably accentuated and, especially if cooled further, will spread to adjacent fingers, the wrist, and the forearm. Itching may be felt near the injured area. Such cooling of the local area may change a mild pain to an almost intolerable ache. This severe pain may be relieved in a few seconds by warming the clamped area. If, however, the clamp is kept cool, the first severe pain moderates somewhat, and as this occurs it is found, by means of skin thermocouples, that the temperature of skin adjacent to the clamp is falling, owing evidently to conduction of heat to the cooler clamp. This means that the temperature difference (thermal gradient) between injured and uninjured tissue is decreasing.

If, instead of cooling the local area alone, the whole hand and clamp are plunged into cool water, a similar intensification of pain is felt, but adaptation occurs and the pain slowly subsides. Complete relief from pain may occur soon after the hand is removed from the water although the skin temperature may now be much below 37°C. Pain is more quickly, and often more effectively, relieved if the influx of warm blood is prevented by occlusion of the brachial artery, presumably because this allows more nearly complete equalization of deep and superficial temperature after both have been lowered by deep cooling. In this type of experiment temperature equalization may presumably be effected at any level below 37°C., but in these experiments it was not attempted below 20°C. It seems that cooling of deep tissues to the temperature of the surface, even when surface temperature is also reduced, may be as effective as heating the normally cooler skin to the temperature of deeper structures. Certainly these two methods for treating pain will alter blood flow in opposite directions, and, in the case of cooling, the slower flow of blood will facilitate the equalization of temperatures of deep and surface tissues. In practice, equalization by heating is more quickly effected. Cooling is apt to increase pain at first, unless it is done very slowly.

It is found that when the clamp on the pain-free, cold-adapted hand is warmed, pain results. This is simply one of the forms of "heat pain." The other form of heat pain, commonly confused with the gradient type, is due to tissue injury. It develops in normal skin heated above about 45°C. (113°F.), but following burns or in other susceptible states, such as erythermalgia, the critical point may be as low as 30°C. Wolf who studied "cold pain," the pain induced by immersion of an extremity in water at a temperature of 18 C. or lower, believed it to be due in part to the thermal gradient set up, since slow cooling, even to 0° C., produced no pain. However, the author believes that cold pain is due entirely to the thermal gradient, whereas Wolf thought that vasospasm might be a contributory factor.

Effects of Thermal Gradients on the Pain from Pulling Hair. When the spring clamp is fastened to the end of a hair and allowed to hang free, a pricking pain may be experienced, starting two or three seconds after application of the clamp, rising in intensity during ten seconds or so and then declining to disappear entirely within perhaps ten or twenty seconds longer. If at any time after applying the clamp, a draft of air, cooler than the skin, is blown across the area, pain, if present, is accentuated, and if absent, may appear as a sharp stab. A similar result may be obtained by touching a cool metal object lightly for only one second against the skin at the periphery of the small area of elevated skin formed by the traction. If the experiment is carefully performed, it can be noted that a sensation of cold, if felt at all, appears immediately on contact of the metal but disappears again after the metal is withdrawn. Sometimes there will be no sense of cold at all, yet the effect to rekindle pain is definite. This finding is important, for it rules out the possibility that pain is affected by temperature through a simultaneous combination of sensations.

When the skin has been cooled, a warm object touched to the edge of the small area of skin under traction may elicit pain, thus demonstrating again that a sufficiently steep thermal gradient, regardless of its direction or of the quality or time relations of the accompanying temperature sensation, may elicit pain or increase pain due to other causes.

Pain in Areas of Hyperalgesia Resulting from Previous Injury. A state of hyperalgesia is readily developed following prolonged clamping of one area, or by repeated sharp blows delivered to the phalanges, or by continued pressure on an interphalangeal joint, or by injection of iodine or other irritant chemical into the skin or periosteum or under the finger nail. In this state pain is absent at rest after the original reaction has subsided, but is elicited by light rubbing of the skin or movement of the joint. It has been found repeatedly that pain, often severe, may be rekindled in such injured tissues by

moderate cooling of the skin, often by as little as 0.2°C. In the cold-adapted hand, pain could be developed by either warming or by further rapid cooling of the skin, the temperature change required being much less than that needed to elicit heat pain or cold pain in adjacent normal tissue at the same temperature. It is thus evident that a thermal gradient, in itself painless in normal tissue, will, when added to a degree of injury, itself painless at the moment, result in a summation phenomenon that may give rise to severe pain.

Effects of Thermal Gradients on Pain Thresholds. Although various gradations of pain can be experienced, it is not possible to compare their intensities objectively or quantitatively. It is, however, possible to measure the minimum strength of stimulus necessary to arouse a just perceptible pain. Hardy, Wolf, and Goodell have developed a method for measuring the pain threshold which gives consistent results and which is in general use for studies on pain, but unfortunately the heat stimulus which they use is not applicable to this problem. Cruder methods have had to be used, involving the application of measured mechanical stimuli, either intermittently or continuously.

The apparatus used for delivering intermittent stimuli was similar to a pile driver. A metal rod weighing 12.5 Gm. with a cross section of 0.25 sq. cm. padded at the end with adhesive tape was arranged to drop vertically through a guide of glass tubing which was marked in centimeters of height above the finger. A thread attached to the upper end of the rod was used to lift it to the desired height and to check its fall after the first bounce when it hit the dorsum of the finger below. The finger to be tested was placed in a groove in a large cork stopper, and the area to be struck was marked with ink, since different areas have widely varying thresholds. In most studies the height of fall necessary to arouse "second pain," which was felt about 1.5 seconds after the blow, was taken as the pain threshold. This was done to avoid the confusion of mixed sensations of touch, pressure, sound, and pain which are experienced at the time of "first pain." A period of from thirty to sixty seconds was allowed for recovery between blows. It was found impossible to obtain reproducible results when the uninjured finger was tested, because of the progressive development of itching and of vague discomfort which interfered with the sharp recognition of the pain from the applied stimulus. However, on the second or subsequent days, when the finger had become hyperalgesic and a little red and swollen, sharply reproducible results could be obtained on some subjects but not on all.

In this experiment the hand was cooled by running tap water for a few seconds before the first threshold was obtained. The skin warmed to 32°C. spontaneously and was further warmed to 38°C. by means of a heat lamp. The last observation followed recooling in water. Just perceptible pain, which vanished within less than a second, was felt at each of the thresholds. But when

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the weight was dropped 15 cm. upon the surface-cooled finger (threshold 3 cm.) a severe pain was produced which persisted in recurrent waves for sixty seconds. Indeed, the maximum pain occurred nearly twenty seconds after the blow was struck. Thermal gradients increase the duration as well as the intensity of a single painful stimulus.

For the measurement of pain thresholds from continuous pressure, hollow copper cylinders of 0.5 square centimeter section were arranged so as to compress the finger web with variable force as determined by a spring balance arrangement supporting a weight which bore upon the upper cylinder. Water perfused through side tubes in the cylinders controlled the temperature of the skin at the points of compression. The results of a typical experiment show how the pressure must be altered in order to maintain a just perceptible ache under various temperatures of the compressed skin.

With cold adaptation the threshold stimulus by either of the two apparatuses used was as high or nearly as high, as for temperature equalization at the higher temperatures.

The apparatuses for producing pain which have been described are not recommended for clinical use, but they have served the purpose of demonstrating that the threshold of pain may be altered several hundred per cent with changes in the thermal gradient.

Relation of the Experimental Findings to Clinical Practice: These studies have no present application to the problems of muscle pain or to the treatment of bacterial infections by heat, or to the pain resulting from burns. It seems highly probable, however, that most pain originating in fascia, joints and skin will respond like the experimental pain studied, and if this proves to be true, it is likely that the present heat treatments for these types of pain will be considerably modified. Careful clinical observation will perhaps show that a few seconds of warming will suffice to give optimum relief from pain, that heating above 37° C. is detrimental, and that exercises to increase joint motion limited by pain should be carried out during the heat treatment rather than afterward. Long-lasting relief from pain will perhaps be best achieved by applying special covering of high insulating value over affected parts to maintain temperature equalization and to prevent rapid surface cooling from sweating or cold air. (Arch. Phys. Med., March '47)

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Stabilization of Penicillin Solutions with Sodium Citrate: Aqueous solutions of penicillin retain their potency at room temperature for a limited period, the stability varying according to the constituents of the different products.

It has been shown that phosphate has a stabilizing effect on the rate of destruction of penicillin by heat, and that the effect is not due to control of pH but to a specific action of the phosphate ion.

The stabilizing effect on sodium penicillin of sodium citrate dissolved in physiological NaCl solution was accidentally discovered when sodium citrate in 0.9 per cent NaCl solution was used as control in experiments with penicillin and citrated blood and found to produce a remarkable stabilizing effect on sodium penicillin. The stabilizing effect is not due to any changes of pH. Sodium citrate proved to be less effective than the combination of sodium citrate and sodium chloride.

Four units of sodium penicillin dissolved in 1 c.c. of a solution consisting of 1 part of M/5 sodium citrate solution and 4 parts of 0.9 per cent NaCl solution, and 4 units of sodium penicillin dissolved in 1 c.c. of M/15 phosphate were tested (1) immediately, (2) after heating at 100° C. for 15 min., and (3) after an hour's heating at 100° C. in the water bath. Under the conditions used, it was found that the stabilizing effect of citrate-NaCl was greater than that of phosphate.

Samples of various penicillin-salt mixtures, each containing 4 units per c.c. were kept in test tubes at 37° C. in the incubator for various periods. Complete sterility was assured in all experiments as proved by controls. The results for (1) a solution of 1 part of M/5 sodium citrate and 4 parts of 0.9 per cent NaCl, (2) 0.9 per cent NaCl, (3) M/15 phosphate, and (4) blood 4 parts and sodium citrate 1 part showed that the loss of potency of the penicillin solutions after three days was zero for the citrate-NaCl, one-third for the phosphate, two-thirds for the blood and citrate, and complete for the saline alone at 48 hours.

Samples containing 4 units of sodium penicillin per cubic centimeter dissolved in citrate-NaCl and phosphate M/15 were ampouled and sterilized at 100° C. for 10 minutes. The ampoules were then kept at room temperature.

In accordance with the findings of others, penicillin-phosphate solutions tolerated sterilization without a considerable loss of potency. In citrate-NaCl solution the loss of activity was very small, even after twenty-three days.

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To ascertain whether changes of penicillin concentration influenced the results, assays were carried out with 1, 2, and 3 units of sodium penicillin per cubic centimeter of the salt mixtures. The potency of the penicillin in citrate-saline mixture showed no appreciable loss after 10 days, whereas it declined very rapidly in the saline only and moderately fast in the phosphate.

In an attempt to find the optimal concentration of citrate effecting stabilization of penicillin, various fractions of molar citrate solutions were tested. The results obtained with M/1, M/5, M/10, M/20, M/50, and M/100 citrate solutions combined with 0.9 per cent NaCl solution showed that there was no correlation between the concentration of the citrate ion and its stabilizing effect on sodium penicillin within the limits of this experiment. But further observations using 0.9 per cent NaCl and sodium-citrate concentrations ranging from M/200 to M/1000 showed that an optimal stabilizing effect was produced by concentrations of M/300 to M/400. After heating at 100° C. for 30 minutes, solutions of sodium penicillin containing 5 units per c.c. were then found to have retained 84 per cent of their potency. The effect of such lower molar concentrations on the stability of penicillin solutions at room temperature is being followed up.

In summarizing, a mixture of sodium citrate in concentrations of M/1 to M/100 and sodium chloride 0.9 per cent in the proportion of 1:4 stabilizes sodium-penicillin solutions at 100° C. and at room temperature. Preliminary work suggests that, with penicillin-sodium solutions up to 5 units per c.c., an optimal stabilizing effect is produced with the sodium-citrate concentrations of from M/300 to M/400. The stabilizing effect of this saline-citrate mixture exceeds that of phosphate. (Lancet, March 29, '47 - L. Hahn)

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Penicillin Therapy of Subacute Bacterial Endocarditis: The studies concerned in this report were begun in July 1943 because of the belief that the previous failure of subacute bacterial endocarditis to respond to penicillin might be due to inadequate dosage and too short a period of treatment for a disease of this character.

To date 38 patients have been treated or are under treatment. The first 34 were reported upon because the "recoveries" had been observed long enough for the authors to be reasonably sure of permanency.

In the management of these patients an attempt was made to establish the approximate date of onset of the disease and the immediately predisposing illness, such as infection of the upper respiratory tract, "influenza,"

or extraction of teeth. No patient was included in the study unless cultures of the blood yielded pathogens, even though clinical findings made the diagnosis likely. Laboratory examinations on the patients' admission to the hospital consisted of: complete blood cell count; urinalysis; culture of urine; Kahn test; determination of the sedimentation rate, blood nonprotein nitrogen and chloride levels, carbon dioxide-combining power, total protein content and albumin globulin ratio; tests of renal function; sulfobromophthalein test of hepatic function; tests of erythrocyte fragility and capillary fragility; and cultures of material from the nose and throat. Roentgenograms of the chest at 2 meters, electrocardiograms and dental roentgenograms of the whole mouth were also made. Electrocardiograms were repeated at weekly intervals. The roentgenogram of the chest at 2 meters was repeated upon the patient's discharge. Blood cell counts, urinalyses, determinations of the sedimentation rate and cultures of the blood were made frequently. Penicillin serum levels were determined and penicillin urinary excretion studied on many of the patients. A high caloric, high protein, high vitamin diet was given. In addition to the administration of a multiple-vitamin capsule of high potency, 100 mg. of thiamine hydrochloride, 50,000 units of vitamin A and 500 mg. of ascorbic acid were given to the patients daily. The authors believe that such supportive treatment is important in a relatively chronic wasting disease of this type. The patients were unselected. No patient was refused treatment because of duration of illness or apparent hopelessness of condition.

Of 34 unselected patients with subacute bacterial endocarditis treated with penicillin, twenty-two (65 per cent) are alive and free of any evidence of the disease from thirteen to thirty-five months after completion of treatment.

The duration of the disease ranged from one and a half to fifty-two weeks before admission to the authors' service.

Streptococcus viridans predominated as the offending organism, but six other organisms were encountered. In vitro sensitivity of the organisms to penicillin in 27 cases ranged from 0.02 to 6.0 units per cubic centimeter.

Administration of penicillin in isotonic solution of sodium chloride by continuous intravenous drip was found superior to intermittent intramuscular injection in the maintenance both of constant adequate blood levels and of the patient's comfort. Five per cent dextrose in isotonic solution of sodium chloride was found much more likely to produce troublesome venous irritation and thrombosis.

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Restriction of the intake of fluids to 800 or 900 c.c. during the waking period resulted in less wide fluctuations of serum penicillin level.

Increasing the dose of penicillin seemed simpler than using para-aminohippuric acid or diodrast to retard the rate of excretion from the kidneys.

No clinical or histologic evidence was found to favor the use of anti-coagulants. The danger of fatal hemorrhage suggests caution in their use.

The success of treatment was judged by clinical, laboratory, and histologic evidence.

Adequate daily dosage over a sufficiently long period is the most important single factor in successful treatment. With the use of continuous intravenous drip, the minimal efficacious dosage is 500,000 units per day with the administration of from 1,000,000 to 2,000,000 units per day or more if clinical criteria dictate or if the disease is of over twelve weeks' duration. Daily dosage of 500,000 or more units at the outset has resulted in recovery of 100 per cent of 16 consecutive patients, as compared with 59 per cent (adjusted figures) in the first 20 patients, in which 7 of the 10 deaths occurred in patients receiving 400,000 units or less. If intermittent intramuscular injection is the only feasible method, minimal doses of 100,000 units at ninety-minute intervals are recommended. Treatment should be continued for not less than four weeks.

Conclusive evidence, either in vitro or clinical, of the synergistic effect of the sulfonamide drugs was found in only one patient, in whom the causative organism was classified as Hemophilus para-influenzae.

The in vitro sensitivity of the organism has little bearing on the outcome of the disease but is a rough guide for the daily dose. A minimal daily dosage of 1,000,000 units or more is recommended when dealing with organisms sensitive to only 0.1 unit or more in vitro. The possibility of the presence of a strain of Str. viridans particularly resistant in vivo should be considered as a cause of failure not otherwise explainable. A minimal daily dosage of 2,000,000 units for this organism seems essential.

The most reliable indexes of successful therapy and adequacy of therapy were found to be the leukocyte count and the sedimentation rate. Sterile cultures of the blood alone cannot be considered conclusive because they do not indicate control of the valvular lesions. These points, as well as daily dosage, in relation to the findings at autopsy will be discussed in detail in a subsequent publication.

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All recovered patients were observed (blood cell counts, sedimentation rates, cultures of the blood, and physical conditions) at weekly intervals during the first month after discharge, thereafter semimonthly for six months and then monthly to date. (Arch. Int. Med., March '47 - W. S. Priest et al.)

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Toxicity of 2,4-Dichlorophenoxyacetic Acid for Experimental Animals: Within the past few months several articles have appeared in the scientific press describing the action and use of 2,4-dichlorophenoxyacetic (2,4-D) acid and its ammonium or sodium salts as herbicides and plant hormones. (See Bumed News Letter of 14 March, 1947, p. 2.) This compound has also been used in orchards to prevent the premature dropping of apples.

However, practically no data have been presented in the literature on the toxicity of this and related compounds. Experiments were performed to determine the toxicity of the free acid and its salts for experimental animals when administered orally, parenterally, and by inhalation.

The investigations disclosed that 2,4-D is a relatively nontoxic compound for experimental animals with an LD_{50} of 375 mg. per Kg. for mice, 1000 mg. per Kg. for guinea pigs, 666 mg. per Kg. for rats, and 800 mg. per Kg. for rabbits when administered orally in aqueous solution. All of these species reacted similarly to the chemical. There was no apparent difference in the toxicity between crude acid and a highly purified preparation, or between the sodium and ammonium salts of the acid.

Monkeys were shown to be able to tolerate 428 mg. per Kg. of 2,4-D when administered intraperitoneally. However, when the material was given in large doses by mouth, one or one and one-half grams, the animals became nauseated and vomited a large portion of the material so that accurate information on the toxicity of the compound administered by the oral route in this species is lacking. Three-fourths of a gram of the material was given to one monkey without the development of vomiting or serious illness. Based on the best data available, which are recognized to be inadequate, monkeys can tolerate single dosages equivalent to 214 mg. per Kg.

In any appraisal of the acute toxicity of a chemical based on data obtained from laboratory animals it should be borne in mind that considerable variation in species susceptibility may occur and that the data obtained cannot always be translated into the toxic doses for humans. In this case, however, all of the laboratory animals tested reacted in a similar fashion to the material as far as could be determined from signs and symptoms which

developed and from the pathological lesions which were present at autopsy. Assuming that man is no more resistant or susceptible than the rabbit or monkey, then the largest tolerable dose for a 75-Kg. man would be 15 Gm. With the exception of the monkey, all of the laboratory animals used were unable to relieve themselves of irritating material since they lacked the vomiting reflex. The experiments conducted in monkeys indicate that the material is a gastric irritant in large doses, so that the possibility of the occurrence of acute poisoning in humans would seem relatively remote because of the large dose which man could presumably tolerate. Assuming that man is no more susceptible than the most susceptible animal tested, the mouse, then the calculated oral LD_{50} for man would amount to approximately 28 Gm.

Subacute intoxication was produced in dogs by giving daily injections of the material over a period of six days. With the administration of smaller doses, 25 mg. per Kg., there was a suggestion that the material had a cumulative action. In contrast with the other species studied, dogs showed a considerable susceptibility to the development of liver damage. Occasional lymphoid necrosis in the lymph nodes, thymus, and spleen occurred especially with high doses. A few animals demonstrated a significant reduction in the number of lymphocytes in the circulating blood. The development of decubitus ulcers and their occasional association with a significant reduction in the leukocyte count was a disturbing observation. Reduction in the leukocyte count did not occur in every case, but its occasional development should direct attention to blood studies in cases of suspected intoxication in man.

Investigations on the subacute toxicity of 2,4-D by the oral route were limited to rats and guinea pigs. Rats were fed varying amounts of the material up to one-tenth per cent by weight of their diet for a period of one month without any significant effect on their food intake, rate of growth, or the development of any characteristic signs of intoxication. Guinea pigs, which were fed 100 mg. per day of the material by stomach tube over a period of twelve days until a total of 1 Gm. of the material had been administered, did not develop characteristic evidence of intoxication. In this particular experiment, nonspecific deaths occurred in approximately the same percentage in both the test and control animals. All of these deaths were believed to result from trauma, associated with the passage of a stomach tube at frequent intervals, inasmuch as none of the test animals developed the typical paralyses or skeletal muscular signs observed in poisoned animals. It was therefore concluded that guinea pigs could tolerate 1 Gm. of 2,4-D in divided doses over a period of twelve days without any harmful effects.

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The experiments to determine the toxicity of the sodium salt of 2,4-D by inhalation tended to indicate that the material was relatively nontoxic when wet or when dry clouds were inhaled. It should be pointed out that in none of these experiments was the average particle size of the aerosol determined, nor the amount of material retained and absorbed by the respiratory tract determined. Further studies on the toxicity of this compound by the respiratory portal of entry will be needed before any final conclusions can be made. In view of the fact that the material did not produce any evidence of lung irritation and that the toxic oral dose of the material for guinea pigs is relatively high, it would tend to indicate that the material would be relatively nontoxic by this route.

2,4-D dissolved in a solvent complex of tributylphosphate and diesel oil has been recommended for use as a herbicide. This particular form of material has the advantage over the aqueous solution in that the tributylphosphate acts as a coagent or synergist to the 2,4-D producing greater plant damage than could be accounted for by the acid alone. The present study did not attempt to determine the toxic or tolerated dose of tributylphosphate alone or of diesel oil alone.

There was no evidence of a synergistic or additive toxic effect when a tolerable amount of 2,4-D was dissolved in the tolerable dose of tributylphosphate oil complex and administered to the experimental animals. Production of chronic poisoning by this material was not attempted. (J. Indust. Hyg. & Toxicol., March '47 - E. V. Hill and H. Carlisle)

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Forwarding of Dental Records of Transferred and Separated Personnel: Alnav 9-47 and Alnav 87-47 have directed the forwarding to BuMed of health records of personnel no longer attached and whose addresses cannot be ascertained.

Because many dental records of transferred or separated personnel have for various reasons accumulated in ships and stations, BuMed has great difficulty in replying to correspondence concerning former naval personnel, especially requests for information from the Veterans Administration. The dental records of transferred personnel whose present duty stations can be ascertained should be forwarded to those stations on the earliest possible date. The dental records of all other transferred or separated personnel should be forwarded to BuMed immediately.

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Appointments in the Medical Corps of the U.S. Navy and U.S. Naval Reserve: Reports from the field indicate that some uncertainty exists concerning the grades to which appointments may be made in the Medical Corps of the U.S. Navy and the U.S. Naval Reserve. The following information is given in order to clarify any misunderstanding that may exist:

Graduates and students of accredited medical schools may apply for appointment to commissioned rank in the U.S. Navy or the U.S. Naval Reserve in the grades listed below. Those interested in such appointments may obtain further information by writing to or inquiring in person at the nearest Office of Naval Officer Procurement, or the Bureau of Medicine and Surgery, Navy Department, Washington 25, D. C.

ENSIGN, HP, (MED), U. S. NAVAL RESERVE. Male students who are enrolled in or accepted for enrollment in the next convening class of an approved medical school and who meet the prescribed age, citizenship, and physical requirements are eligible for appointment to the probationary rank of Ensign, HP, in the U. S. Naval Reserve. Under the current program, this appointment carries with it NO OBLIGATIONS for active Naval service notwithstanding previous V-12 training, nor is the appointee required to accept superseding appointment in the Medical Corps of the U. S. Navy or the U. S. Naval Reserve upon graduation from medical school. This commission is subject to revocation by reason of scholastic failure or for other reason at the discretion of the Secretary of the Navy, and in any event, becomes subject to revocation upon completion of medical school education whether or not the appointee accepts superseding appointment in the Medical Corps of the U. S. Navy or the U. S. Naval Reserve.

ASSISTANT SURGEON, U. S. NAVAL RESERVE. All male fourth-year students of good scholastic standing enrolled in approved medical schools and male graduates of such schools engaged in intern training or civilian practice (after internship) who meet the prescribed age, citizenship, and physical requirements are eligible to apply for appointment to the grade of Assistant Surgeon with the rank of Lieutenant (junior grade) in the Medical Corps of the U. S. Naval Reserve. Selected student candidates become eligible for appointment upon completion of medical school, whereas acceptable graduate candidates are issued immediate appointment. Appointment to this status (or to any other grade) in the Medical Corps of the U. S. Naval Reserve carries NO OBLIGATION for active Naval service except on a purely voluntary basis notwithstanding the extent of any past V-12 training or affiliation. Those former V-12 students who graduated from medical school prior to 1 July 1946 are excluded from this provision and will be required to perform active duty upon acceptance of their appointments. Doctors whose age, professional experience, and academic seniority justify a more senior grade may make application for appointment to grades above that of Assistant Surgeon, U. S. Naval Reserve.

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ACTING ASSISTANT SURGEON, U. S. NAVY (INTERN). All male fourth-year students of good scholastic standing enrolled in approved medical schools in the United States and Canada who meet prescribed age, citizenship, and physical requirements are eligible to apply for appointment to the grade of Acting Assistant Surgeon with the rank of Lieutenant (junior grade) in the Medical Corps of the U. S. Navy for intern training in a Naval Hospital. Selected candidates will be issued an appointment and orders to active duty for internship upon receipt in the Department of a certificate from the Dean or Registrar of their school to the effect that they have completed their medical school education. Acting Assistant Surgeons are under no obligation to continue in the Naval Service beyond completion of prescribed course of intern training (see Procurement Bulletin No. 9-47 for complete directions on service obligations of Acting Assistant Surgeons). The grade of Acting Assistant Surgeon does not exist in the U. S. Naval Reserve, nor is intern training in the U. S. Navy extended to members of the Medical Corps of the U. S. Naval Reserve.

ASSISTANT SURGEON, U. S. NAVY. Graduates of approved medical schools who have completed intern training in an accredited hospital or who will complete such training within four months of a date set for examination and who meet prescribed age, citizenship, and physical requirements are eligible to apply for examination for appointment as Assistant Surgeon with the rank of Lieutenant (junior grade) in the Medical Corps of the U. S. Navy. Candidates for this grade are required to appear before Boards of Medical Examiners and Supervisory Examining Boards at a Naval Hospital on a prescribed date to establish their physical and professional qualifications for appointment. The acceptability of candidates will be finally determined by Boards convened in the Navy Department from a review of reports of examination conducted in the field (the next examinations for Assistant Surgeon, USN, are scheduled for June 23 to 27, 1947 and thereafter for October 6 to 10, 1947). The grade of Assistant Surgeon represents the lowest permanent grade in the Medical Corps of the U. S. Navy and might be classed as the starting point of continuous active service for the physician who elects a career in Naval medicine.

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American Board of Physical Medicine Established: Announcement has recently been made that the establishment of the American Board of Physical Medicine has been approved by the Advisory Board for Medical Specialties of the Council on Medical Education and Hospitals, American Medical Association, with the understanding that it would be an affiliated board of the American Board of Internal Medicine until such time that it is recommended that an independent status be granted. As an affiliated board, it will not be necessary for the physician who qualifies in physical medicine to qualify also in internal medicine as a requisite for membership.

Requirements for candidates for this board have not been completed, but it is anticipated that the first examination will probably be conducted in September of this year. Additional details concerning this new specialty board will be announced as they become available.

This announcement should be of particular interest to those naval medical officers who are contemplating specializing in this rapidly expanding field of medical practice. There is an urgent need at the present time in the Navy for medical officers with this specialty training. To this end, applications are desired from medical officers of the Regular Navy for a fellowship in physical medicine at the Mayo Clinic, Rochester, Minn. The fellowship will be of twelve months' duration and will begin on 1 July 1947, and quarterly thereafter. Requests should be submitted in accordance with the BuMed News Letter dated 24 May 1946, page 23, and may be made by dispatch. (Professional Div. BuMed)

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Residencies Available in Neuropsychiatry: Of interest to those young medical officers contemplating further study in the field of neuropsychiatry will be the establishment of six accredited residencies for Navy medical officers in the Naval Medical Unit, U.S. Public Health Service Hospital, Fort Worth, Texas.

The Navy has been caring for some of its psychotic patients at the Public Health Service Hospital in Fort Worth since 1942. Since July 1946 all Navy patients requiring special psychiatric care have been transferred to Fort Worth for treatment and disposition. This hospital now serves the function, with respect to psychotic Navy patients, once served by St. Elizabeth's Hospital, Washington, D.C.

The Public Health Service and the Navy are cooperating in the development of a training program for Navy and Public Health doctors which will be among the best offered anywhere. It is expected that outstanding specialists in the field of neuropsychiatry will visit Fort Worth periodically to participate in the training schedule.

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Requests for these residencies from medical officers of the regular Navy are desired to reach BuMed prior to 1 June 1947 and may be made by dispatch. (Professional Div., BuMed)

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Training in Neuropsychiatry: In order to furnish more information to medical officers desiring to enter training in neuropsychiatry the following information received from the American Board of Psychiatry and Neurology is presented:

Suggested 3-Year Full-Time Training Program for Psychiatrists

1. One year of in-patient work with an adequate variety of psychiatric conditions.

2. Six months of full-time out-patient clinic work, or its equivalent, with emphasis on the study and treatment of psychoneurotic patients, and with a minimum of 20 interviews per week per resident.

3. Six months of neurology with one-half time clinical and one-half time basic.

4. Six months of half-time service in the psychiatric aspects of general medical and surgical conditions.

5. Six months of half-time child psychiatry and experience in working with psychologists and psychiatric social workers.

6. Six months in specialized institutional psychiatry dealing with feeble-mindedness, epilepsy, forensic psychiatry, penology, drug and alcohol addiction, and so forth.

7. During these 3 years it is recommended that there be available teaching ward rounds, staff conferences, seminars, journal clubs, adequate psychiatric texts and periodicals, and participation in some phase of psychiatric investigation.

8. During these 3 years there should be adequate instruction in the basic psychiatric concepts as covered in the material recommended in the syllabus of the American Board of Psychiatry and Neurology.

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9. In institutions in which there is no full-time senior staff there should be in the aggregate a minimum of 15 hours a week of service by senior attending staff in capacities instructive to the resident staff.

10. In planning training programs of one, two, or three years may be worked out to include various fractions of the foregoing suggested items. It is not considered necessary that any program of instruction be followed rigidly. For instance, a resident may devote a full day or half day a week to the psychiatric aspects of medical and surgical conditions for a year or so while assuming major clinical responsibilities in a psychiatric hospital.

The purpose in suggesting the foregoing program is to indicate a desirable spread of experience in the training of a psychiatrist.

In the last issue of the Bumed News Letter an announcement was made of the availability of several approved residencies in this specialty. Requests for these residencies are desired from medical officers of the regular Navy in accordance with Bumed News Letter dated 24 May 1946.

(Professional Div., BuMed)

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Residencies in Orthopedic Surgery at U. S. Naval Hospitals: The Bureau of Medicine and Surgery has just been informed that the American Board of Orthopedic Surgery will give credit for residencies in orthopedic surgery in Naval hospitals exactly as outlined in the Educational Number of the Journal of American Medical Association (August 17, 1946).

This information is furnished because several discrepancies in this connection have been called to the attention of the Bureau. (Professional Div., BuMed)

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Postgraduate Training in Photofluorographic Interpretation: The Bureau of Medicine and Surgery announces that the next class in Photoflurographic Interpretation will begin 2 June 1947 at the Naval Medical School, Bethesda, Md. The course will be of six weeks' duration and may be extended from two to four months, depending on the vacancies in the various photofluorographic units.

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Photofluorographic interpretation provides an excellent introduction to two specialties, radiology and internal medicine (chest diseases).

A service agreement is not necessary. Reserve medical officers are eligible for this training provided that they have sufficient obligated service to make possible at least one year of active duty after the completion of the course. Requests are to be submitted in accordance with Bumed News Letter dated 24 May 1946 and may be made by despatch. (Professional Div., BuMed)

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Postgraduate Training in Electroencephalography: The next class in Electroencephalography will convene at the U.S. Naval Medical Center, Bethesda, Md., sometime in August 1947. This course is of six months' duration and does not require a service agreement. It is believed that the younger members of the Medical Corps will find electroencephalography to be a fascinating field, and it does not require previous training in psychiatry and neurology. Some preliminary experience in these fields would be of benefit, however. This course will provide excellent training which will add to the professional record of any medical officer who strives toward certification by certain Specialty Boards. Requests are desired from medical officers of the regular Navy to reach BuMed prior to 1 June 1947 and may be submitted by despatch. Reserve medical officers may apply for training in electroencephalography provided that they express a desire for transfer to the regular Navy and have sufficient obligated service. Further inquiries are invited from interested medical officers. (Professional Div., BuMed)

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Guest Lecturers at the U. S. Naval Dental School, National Naval Medical Center, Bethesda, Maryland: The following are the guest lecturers and their subjects scheduled during May 1947:

May 2 - Harold W. Krogh, D.D.S. - "Roentgenographic Findings Pertaining to Oral Surgery." Doctor Krogh is the Chief of the Oral Surgery Services of Episcopal Eye, Ear & Throat, Emergency, and George Washington University Hospitals. This lecture will consist of a chalk talk regarding roentgenographic diagnosis in the practice of oral surgery. Conference Room 244 at 1300.

May 9 - Captain L. D. Mitchell, Jr., DC. USN - "Dental Administration - Duties of Staff Dental Officers" Conference Room 244 at 1500.

(Not Restricted)

May 16 - Samuel C. Miller, D.D.S. - "Traumatic Occlusion, Its Etiology, Detection and Correction Including Motion Pictures on the Technic of Equilibration of Occlusion." Doctor Miller has been associated with the department of periodontia at New York University since 1925 and is now Associate Professor and Chairman of the Periodontial Department of that School. He is the author of numerous articles on this and allied subjects as well as co-author of Practical Periodontia and the author of Oral Diagnosis and Treatment and the Textbook of Periodontia. Conference Room 244 at 1300.

May 23 - Daniel E. Ziskin, D.D.S. - "The Differential Diagnosis of Necrotising Mouth Lesions and the Mouth Manifestations of Endocrine Disturbances." Doctor Ziskin is Head of the Division of Graduate Studies and Chairman of the Research Committee at Columbia University. He has been engaged in teaching the diagnosis of mouth diseases since 1918 and has been actively engaged in endocrine research since 1930. The lecture will be demonstrated with kodachrome slides. Conference Room 244 at 1300. (Dental Div., BuMed)

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(Not Restricted)

Reactivation of the Naval Reserve: The Bureau of Medicine and Surgery has received communications from a large number of Reserve medical officers who express exceptionally keen interest in the Medical Department of the Navy, and urge the immediate adoption of a program that will assure Reserve medical personnel on inactive duty of the fact that they are an integral part of the Naval establishment.

In order to reactivate a strong Medical Reserve, in keeping with the Postwar Reserve Program, it will be necessary to reorganize Medical Specialists' Units and to obtain factual information on the professional qualifications of Reserve medical officers. In this connection the Navy Department has authorized a billet for a Reserve medical officer on full-time active duty in the Bureau of Medicine and Surgery and in each Continental Naval District. The duty of these Reserve officers is to assist in accomplishing the organization of an efficient and well planned Reserve Component of the Medical Department of the Navy.

Reserve medical officers (inactive), all of whom are on a purely voluntary basis, are asked to contact their Naval District Commandant and volunteer their assistance in connection with the promulgation of the Reserve recruiting publicity program, OPERATION NAVAL RESERVE (see page 2)

(Not Restricted)

which is planned to play an important part in the reactivation of the Naval Reserve.

Additional information concerning the medical Reserve program may be obtained by addressing the Bureau of Medicine and Surgery, Navy Department, Washington 25, D. C. (Personnel Div., BuMed)

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(Not Restricted)

Policy of BuMed re Duty with Materiel Aspects of Medical Department Logistics: An article outlining the policy of the Bureau of Medicine and Surgery concerning assignments to duty connected with medical materiel was contained in the 28 March issue of the Bumed News Letter.

It is believed that officers who may desire to take advantage of the opportunities offered by this kind of duty and who have not yet seen this article will be interested in it. (Personnel Div., BuMed)

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(Not Restricted)

Mayo Clinic Fellowships in Physical Medicine Available: See information contained in notice on page 27 announcing the establishment of the American Board of Physical Medicine.

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(Not Restricted)

Public Health Foreign Reports:

Disease	Location	Date	No. of Cases
Cholera	Siam (Thailand)	Feb. 2-8, '47	166 (106 fatal)
Plague	Brazil	June '46	19 (1 fatal)
		July '46	25 (6 fatal)
		August '46	38 (8 fatal)
	Burma	Feb. 2-8, '47	125 (95 fatal)
	Java (Central)	1946	2409 fatal
	Peru	October	20 (2 fatal)
		November	26 (2 fatal)

(Not Restricted)

Public Health Foreign Reports (Cont.)

Disease	Location	Date	No. of Cases
Smallpox	Malay States (Federated) Trengganu	Feb. 16-22, '47	218 (41 fatal)
(alastrim)	Uruguay	Feb. 19, '47 (date rep.)	138
Typhus Fever	Colombia	January '47	127 (3 fatal)
Yellow Fever	Colombia	Dec. 30, '46-Jan. 22, '47	15 fatal

(Pub. Health Reps., March 21, '47)

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BuMed-21-dg; A3-4/EN 4 April 1947 (Not Restricted)

To: Assistant Chiefs of Bureau and Chiefs of Divisions, BuMed

Subj: Assistant Chief of Bureau for Dentistry and Chief of Dental Division, Code 6; establishment of.

Refs: (a) BuMed-21-dg, A3-4/EN directive dtd 26 March 1947; Establishment of General Inspector, Dental Service, Code 15, and Disestablishment of Assistant Chief of Bureau for Dentistry, Code 6.

(b) BuMed-E-DG, A3-4/EN directive dtd 20 Aug 1946; Reorganization of Dental Functions and Establishment of a Dental Division, Bureau of Medicine and Surgery.

1. References (a) and (b) are further modified as follows:

Rear Admiral A. W. Chandler, (DC) USN is designated Assistant Chief of Bureau for Dentistry and Chief of Dental Division. Code 6 is reassigned to this office.

--BuMed. C. A. Swanson

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Circular Letter 47-42 - Not released in time for inclusion.

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Circular Letter 47-43 7 April 1947 (Not Restricted)

To: Comdts, NDs and RivComs

Subj: Contracts for medical services for officers and enlisted men attached to Naval Reserve Officers' Training Corps Units.

Refs: (a) Article 1189, N.R.
(b) Part III, Chapter I, Manual Medical Department.

This letter from the Chief of BuMed (1) points out that the majority of colleges and universities throughout the country where NROTC units have been established have a Student Health Plan of some kind for the care and treatment of minor injuries and illnesses suffered by their students and (2) suggests that, through the office of the Commandant of each Naval District, steps be initiated with the various schools concerned toward the setting up of an arrangement, if agreeable to the school, for furnishing this type of medical care to NROTC personnel. Instructions are given for preparing requisitions, etc. It is necessary that appropriate entries be made in the health records of each person furnished treatment under such contracts. Treatment or services required by the staff personnel not covered by contract should be procured on Form U basis as per reference (b).

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Circular Letter 47-44 8 April 1947 (Not Restricted)

To: All Ships and Stations

Subj: First Aid Kits in Aircraft

This letter from the Chief of BuMed points out that three types of aircraft first aid kits are procured and supplied by the Bureau of Medicine and Surgery with the intention that first aid equipment shall be available to all flying personnel in the event of injuries sustained during flight, crashes, ditching, or bail-out:

Kit, First Aid, Aeronautic, Stock No. 9-196-650, which is installed in aircraft;
Kit, First Aid, Aviator, Camouflaged, Stock No. 9-197-675, which is worn on the person; and
Kit, First Aid, Pneumatic Life Rafts, Camouflaged, Stock No. 9-227875, for aircraft pneumatic life rafts.

(Not Restricted)

Instructions are given for the uses and quantity distribution of each kit. A full copy of this letter will be contained in the 15 April 1947 issue of the Navy Department Bulletin.

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Circular Letter 47-45 8 April 1947 (Not Restricted)

To: MedOfCom, All U.S. Naval Hospitals

Subj: Hospital Accounting Instructions, Changes in

Ref: (a) Hospital Accounting Instructions

Encl: 1. (HW) Two (2) Copies, pages 8 to 11, 39 to 41, 44, 45, and 60 to 67.
2. (HW) Two (2) Copies, pages 117 (d), 117 (e) and 125.
3. (HW) Two (2) Copies of corrections to be made in ref (a).

This letter from the Chief of BuMed contains directions for the use of the enclosures which modify the existing Hospital Accounting Instructions, reference (a).

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Circular Letter 47-46 14 April 1947 (Not Restricted)

To: All Ships and Stations

Subj: Bureau of Medicine and Surgery Section, Catalog of Navy Material; Declassification of.

1. Subject publication is hereby declassified, effective immediately.

--BuMed. C. A. Swanson

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Circular Letter 47-47 14 April 1947 (Not Restricted)

To: MedOfsCom, NavHosps

Subj: Operation of Ship's Service Laundries in Conjunction with Naval Hospital Laundries.

Ref: (a) OinC, Navy Ship's Store Office, ltr, ND13/NH14/S35, Y:kbs, of 12 Mar 1947.

Encl: 1. (HW) Copy of reference (a).

This letter from the Chief of BuMed states that comments and recommendations are desired relative to a proposal, reference (a), having to do with the operation of Ship's Service Laundries in conjunction with Naval Hospital Laundries. Certain points to be considered are listed.

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Circular Letter 47-48 16 April 1947 (Not Restricted)

To: MedOfsCom, NavHosps

Subj: NAVMED-103 (Hospital Bed Capacity--Quarterly Report), Revision of.

This letter from the Chief of BuMed states that the revised form which can be procured from the nearest District Publication and Printing office is to become effective 1 May 1947.

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ALNAV 80 17 March 1947 (Not Restricted)

Subj: Sodium Chloride Isotonic Solution.

Alnav 30-47 canceled. Survey and destroy all units of sodium chloride isotonic solution 1,000 c.c., 6s, stock number 1-429-500, BuMed Section Catalog of Navy Material with lot numbers preceding 10299F manufactured by Don Baxter, Incorporated, Glendale, California. All intravenous solutions shall be carefully inspected prior to use. Solutions containing particulate matter shall not be administered.

--SecNav. James Forrestal

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